allergen-specific IgE antibodies (Boulet, et al. (1997) 155:1835-1840; Fahy, et al. (1997) *American J Respir. Crit. Care Med.* 155:1828-1834; Demoly, P. and Bousquet (1997) *J Am J Resp. Crit. Care Med.* 155:1825-1827), or by the pan specific anti-allergy therapy described in U. S. Serial No. 08/090,375 filed June 4, 1998, by M. Caplan and H. Sosin. Therapy with the modified allergen can also be administered in combination with an adjuvant such as IL 12, IL 16, IL 18, IFNγ.--

Remarks

The above amendments to the claims:

Claims 14-29 have been cancelled. Cancellation of claims 14-29 is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserves the right to file one or more continuing applications hereof containing these cancelled claims.

New claims 37-59 have been added to more particularly recite the invention. Support for these new claims can be found throughout the specification and claims as originally filed.

No new matter has been added by way of these new claims.

The above amendments to the specification:

The specification has been amended to reflect all the priority claims that were made on the Substitute Declaration of the parent application 09/141,220 (a copy of which was filed with the present divisional application 09/478,668 on January 6, 2000).

The typographical error on page 15, line 20 (referred to by the Examiner in ¶ 7 of the July 19, 2001 Office Action) has been corrected.

No new matter has been added to the specification by way of these amendments.

Objections to and rejection of claims 14-29:

The Examiner has raised objections and rejections against claims 14-29 under 35 U.S.C. § 112, § 102(b) and § 103(a). Applicant respectfully points out that claims 14-29 have been cancelled. Cancellation of claims 14-29 obviates these objections and rejections. Nonetheless, in an attempt to further prosecution towards allowance, the objections and rejections applied in the Office Action are addressed below with respect to new claims 37-59.

Priority filing date:

The Examiner states in his Office Action that claims 14, 16-18, and 22-24 are entitled to the priority filing date of the parent application serial number 09/141,220 (filed August 27, 1998), but not the priority filing date of earlier provisional applications serial number 60/073,283 (filed January 31, 1998), and 60/074,633, 60/074,624, 60/074,590 (all filed February 13, 1998). In particular, the Examiner states that there is no support in the earlier provisional applications for limitations to a modified allergen that "activates T cells" and "binds IgG".

Applicant submits that new claims 37-59 are entitled at least to the filing date of prior application serial number PCT/US96/15222 entitled "Peanut Allergens and Methods" filed September 23, 1996 (the '15222 application).

For example, with respect to new claim 37 (that lacks "activates T cells" or "binds IgG" limitations), the '15222 application disclosed:

- the Ara h 1 amino acid sequence (see, for example, Table 35 on pages 172);
- IgE epitopes within Ara h 1 (see, for example, Table 22 on page 135);
- modifications within Ara h 1 IgE epitopes that disrupt IgE binding (see, for example, Figure 26);
- the Ara h 2 amino acid sequence (see, for example, Table 36 on page 173);

- IgE epitopes within Ara h 2 (see, for example, Table 26 on page 152); and
- modifications within Ara h 2 IgE epitopes that disrupt IgE binding (see, for example, Figure 33).

The '15222 application also discusses the use of modified Ara h 1 or Ara h 2 protein allergens to reduce peanut allergy (see, for example, page 117, lines 13-21; page 157, lines 19-21; page 174, lines 1-13). Furthermore, the application discusses application of this strategy of modifying IgE binding sites to other natural protein allergens (see, for example, page 174, lines 14-19).

Given that the '15222 application provides a discussion of the desirability of generating modified protein allergens wherein "IgE binding to the modified protein allergen is reduced as compared with IgE binding to the natural protein allergen", provides at least two examples of such modified protein allergens, and provides teachings sufficient to enable those of ordinary skill in the art to generate modified versions of other protein allergens (the Examiner is referred to the following section for a more detailed discussion of the enablement requirement), the application fully supports new claim 37, and new claim 37 is therefore entitled to the '15222 application's September 23, 1996 filing date.

Furthermore, given that the '15222 application provides a discussion of the desirability of generating modified protein allergens that "retain the ability to activate T-cells" (see, for example, page 74, lines 1-6) and/or "retain the ability to bind IgG" (see, for example, page 126, line 28 to page 127, line 13), and that the methods for measuring the activation of T-cells and IgG binding would have been obvious to one of ordinary skill in the art at the time the invention was made, Applicant further submits that claims that include either or both of these limitations (e.g., new claims 43 and 44) are also fully supported by the '15222 application and are therefore also entitled to the '15222 application's September 23, 1996 filing date.

Rejection under 35 U.S.C. § 112 ¶ 1:

The Examiner states in his Office Action that the specification of the present divisional application 09/478,668 (the '668 application) does not enable one of ordinary skill in the art to make and use the invention commensurate in scope with claims 14 and 28. In particular, the Examiner states that there is insufficient enablement for claims to *any* protein allergen modified according to the present invention.

In supporting his rejection, the Examiner cites *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) and lists the scope of the claim, the amount of direction and guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation as particularly relevant to his rejection.

Applicant disagrees with the Examiner and submits that new claims 37 and 51 (that replace claims 14 and 28, respectively) are fully enabled by the specification of the '15222 application.

As acknowledged by the Examiner, the present specification provides explicit exemplification of modified peanut allergens and methods of preparing them. The specification demonstrates that such modified peanut allergens have reduced IgE binding. Thus, the specification teaches that it is possible to modify a natural protein allergen to reduce IgE binding, provides successful evidence of such modification, and gives precise guidance for how to accomplish the modification. While it is true that the examples presented in the specification are peanut allergens, the specification clearly states that its teachings are applicable to other natural protein allergens. Those of ordinary skill in the art, having read the present specification, would not require undue experimentation to prepare other modified protein allergens with reduced IgE binding.

The situation in the present case is similar to that described in *In re Wands* (858 F2d 731, (Fed. Cir. 1988)), one of the seminal cases on the enablement standard. In *Wands*, the issue was whether the Wands specification was enabling of claims to *any* antibody having a certain affinity for hepatitis B surface antigen, given that the specification provided examples of only three antibodies. The Court held that the description in the Wands specification was sufficient because, even though many difficult experimental steps (i.e., immunization of animals, isolation of lymphocytes from fused animals, fusion of isolated lymphocytes with myeloma cells, screening of hybridomas to identify those that make appropriate antibodies, and isolation of such antibodies) are required, those of ordinary skill in the monoclonal art expect to undertake many such steps and "are prepared to screen negative hybridomas in order to find one that makes a desired antibody" (8 USPQ2d 1400, 1407). In essence, once *Wands* demonstrated that high affinity antibodies *could* be obtained, those of ordinary skill in the art could turn the experimental crank with a reasonable expectation that they too would be able to isolate such antibodies.

Similarly, in this case, the inventors have demonstrated that a modified protein allergen with reduced IgE binding *can* be prepared. Those of ordinary skill in the art can now perform the necessary steps (e.g., use patient sera to identify IgE binding epitopes, modify a protein sequence to alter identified IgE binding epitopes; and screen modified proteins to identify those with reduced binding) with a reasonable expectation that they too will be able to obtain modified protein allergens. There is no particular magic in the sequence of a peanut allergen; the inventive principles, as discussed in the present application, apply to other natural protein allergens as well.

Rejections under 35 U.S.C. § 112 ¶ 2:

Applicant submits that the meaning of the term "compound" in new claim 54 (that replaces cancelled claim 19) is clear and definite. The compound of new claim 54 is defined within the body of that claim as *any* compound that reduces IgE binding to a natural protein

allergen when covalently or non-covalently bound to at least one IgE epitope of the natural protein allergen. This definition is supported by the discussion found on page 13, lines 4-11 of the '668 application and is further clarified by the inventive identification methods that are described on pages 13-15 of the '668 application.

New claim 47 (that replaces cancelled claim 24) relates to "immune stimulatory sequences" and defines the sequence as "containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response" as discussed on page 7, line 8-11 of the '668 application.

New claim 51 (that replaces cancelled claim 28) does not claim protein allergens obtained from birds.

New claim 47 (that replaces cancelled claim 24) claims "in combination, the modified protein allergen of claim 37 and an adjuvant".

Rejection of claims under 35 U.S.C. § 102(b) and § 103(a):

The Examiner rejected claims 14-23, and 25-29 under 35 U.S.C. § 102(b) as being anticipated by Burks et al. (*Eur. J. Biochem.* 245:334-339, April 1997); and claims 14 and 24 under 35 U.S.C. § 103(a) as being unpatentable over Burks et al. (*supra*) in view of Hoyne et al. (*Immunology and Cell Biology* 74:180-186, 1996).

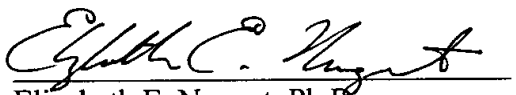
As described herein, the '15222 application fully supports new claims 37-59, and new claims 37-59 are therefore entitled to the '15222 application's September 23, 1996 filing date. Since the cited Burks et al. reference applied in these rejections was not published until April 1997, it cannot anticipate new claims 37-59.

As required, attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made". For the Examiner's convenience, also attached hereto is an Appendix showing all pending claims as amended remaining in this application.

Conclusion

Based on the arguments presented above, it is submitted that the pending claims, as amended herein, are allowable over the art of record. Applicant would also like to thank the Examiner for his thoughtful comments and careful consideration of the case. If a telephone conversation would help expedite prosecution of this case, please do not hesitate to contact the undersigned at (617) 248-5175. Additionally, please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,



Elizabeth E. Nugent, Ph.D.
Registration No. 43,839

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000
Dated: September 19, 2001

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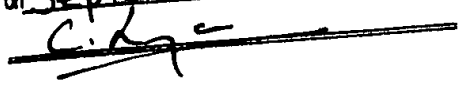

Version with markings to show changes made

In the claims:

Claims 14-29 have been cancelled.

Claims 37-59 have been added.

In the specification:

The paragraph beginning on line 6 of page 1 has been amended as follows:

This is a divisional of Serial No. 09/141,220, filed August 27, 1998, which claims priority to U.S. Serial No. 60/074,590 filed February 13, 1998, entitled "Mutagenized IgE-Binding Epitopes for Ara H 1", by A. Wesley Burks, Jr., Ricki M. Helm, Gael Cockrell, Gary A. Bannon, J. Steven Stanley, and David Shin; U.S. Serial No. 60/074, 624 filed February 13, 1998, entitled "Peanut Allergen Ara H 3" by A. Welsey Burks, Jr., Hugh Sampson, Gary A. Bannon, Shau-Ku Huang, and Patrick A. Rabjohn; U.S. Serial No. 60/074,633 filed February 13, 1998, entitled "Mutagenized IgE-Binding Epitopes for Ara H 2" by A. Wesley Burks, Jr., Ricki M. Helm, Gael Cockrell, Gary A. Bannon, J. Steven Stanley, and Nina King; U.S. Serial No. 09/240,557 filed January 29, 1999, which claims priority to U.S.S.N. 60/073,283 filed January 31, 1998; U.S. Serial No. 09/241,101 filed January 29, 1999, which claims priority to U.S.S.N. 60/073,283 filed January 31, 1998; U.S. Serial No. 09/248,673 filed February 11, 1999, which claims priority to U.S.S.N. 60/073,283 filed January 31, 1998; and under 35 U.S.C. §§ 120 and 371 to PCT/US96/15222 entitled "Peanut Allergens and Methods" filed September 23, 1996, by University of Arkansas, and U.S. Serial No. 08/717,933 filed September 23, 1996.

The paragraph beginning on line 12 of page 15 has been amended as follows:

Therapy or desensitization with the modified allergens can be used in combination with other therapies, such as allergen-non-specific anti-IgE antibodies to deplete the patient of allergen-specific IgE antibodies (Boulet, et al. (1997) 155:1835-1840; Fahy, et al. (1997) *American J Respir. Crit. Care Med.* 155:1828-1834; Demoly, P. and Bousquet (1997) *J Am J Resp. Crit. Care Med.* 155:1825-1827), or by the pan specific anti-allergy therapy described in U. S. Serial No. 08/090,375 filed June 4, 1998, by M. Caplan and H. Sosin. Therapy with the modified allergen can also be administered in combination with an adjuvant such as IL 12, IL 16, IL 18, ~~IFN-ξ~~ IFNγ.

Appendix

37. A modified protein allergen whose amino acid sequence is substantially identical to that of a natural protein allergen except that about 10 to 17 % of the amino acids have been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the natural protein allergen, the at least one IgE epitope being one that is recognized when the natural protein allergen is contacted with serum IgE from an individual that is allergic to the natural protein allergen.

38. The modified protein allergen of claim 37 wherein about 10 to 17 % of the amino acids have been modified in all the IgE epitopes of the natural protein allergen.

39. The modified protein allergen of claim 37 wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the natural protein allergen.

40. The modified protein allergen of claim 37 wherein at least one modified amino acid is located within a central portion of the at least one IgE epitope, the central portion including about 40 % of the amino acids of the at least one IgE epitope.

41. The modified protein allergen of claim 37 wherein at least one amino acid in the at least one IgE epitope of the natural protein allergen has been modified by substitution.

42. The modified protein allergen of claim 41 wherein at least one hydrophobic amino acid in the at least one IgE epitope of the natural protein allergen has been substituted by a neutral or hydrophilic amino acid.

43. The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to activate T cells.

44. The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to bind IgG.

45. The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to initiate a Th1-type response.

46. The modified protein allergen of claim 37 wherein the modified protein allergen is a portion of the natural protein allergen.

47. In combination, the modified protein allergen of claim 37 and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ, and immune stimulatory oligodeoxynucleotide sequences containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response.

48. The modified protein allergen of claim 37 wherein the modified protein allergen is made in a transgenic plant or animal.

49. The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of plants and animals.

50. The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells.

51. The modified protein allergen of claim 37 wherein the natural protein allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish,

crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, and natural latexes.

52. The modified protein allergen of claim 37 wherein the natural protein allergen is a peanut protein selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.

53. The modified protein allergen of claim 37 made by the process of:

identifying at least one IgE epitope in a natural protein allergen;

preparing at least one modified protein allergen whose amino acid sequence is substantially identical to that of a natural protein allergen except, that about 10 to 17 % of the amino acids have been modified in the at least one IgE epitope;

screening for IgE binding to the modified protein allergens by contacting the modified protein allergens with serum IgE taken from at least one individual that is allergic to the natural protein allergen; and

selecting a modified protein allergen with decreased binding to IgE as compared to the natural protein allergen.

54. In combination, a natural protein allergen and a masking compound, the masking compound being covalently or non-covalently bound to at least one IgE epitope of the natural protein allergen in such a way that IgE binding is reduced as compared with IgE binding to the natural protein allergen in the absence of the masking compound, wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE taken from an individual that is allergic to the natural protein allergen.

55. The combination of claim 54 wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the natural protein allergen.

56. The combination of claim 54 wherein the masking compound is an antibody that binds non-covalently to the at least one IgE epitope.

57. The combination of claim 54 wherein the combination retains the ability to activate T cells.

58. The combination of claim 54 wherein the combination retains the ability to bind IgG.

59. The combination of claim 54 wherein the combination retains the ability to initiate a Th1-type response.